British Association of Dermatologists

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Journal:	*British Journal of Dermatology*
Manuscript ID	Draft
Manuscript type:	Commentary
Date Submitted by the Author:	n/a
Complete List of Authors:	Bottomley, Matthew; University of Oxford, CAMS Oxford Institute; Oxford University Hospitals NHS Foundation Trust, Oxford Kidney and Transplant Unit
Keywords:	Squamous cell carcinoma, Immunosuppression, Outcome measurement

Abbreviated Abstract:

A commentary on GÃ³mez-TomÃ¡s et al's article, discussing key findings and next steps in improving immunosuppression management in the setting of post-transplant skin cancer.

Conflicts of interest:

No

Data availability:

No new data were generated or analysed in support of this commentary.

Ethics Approval:

Ethics Confirmation:

N/A

Ethics Details:

N/A

Funding:

Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Science (CIFMS), China, (Grant / Award Number: '2024-I2M-2-001-1')

Skin Cancer in Transplant Recipients: time to revisit immunosuppression trials?

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Word count: 471 words

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In this issue of BJD, Gómez-Tomás *et al* present a robust ten-year, single-centre study of 1,055 organ transplant recipients (OTR), exploring the link between immunosuppressive regimens and skin cancer risk.[1] Skin cancer is the most common malignancy in OTR, affecting up to half of patients over time, with squamous cell carcinoma (SCC) carrying the greatest risk of incidence, recurrence and metastasis.[2]

In this sun-exposed Spanish cohort, Gómez-Tomás *et al* reported that skin cancer occurred in approximately one in eight patients, with SCC accounting for three-quarters of lesions. A key strength of this study was the meticulous documentation of immunosuppressive regimens during the follow-up period, enabling time-adjusted analyses rarely achieved in prior research.

The findings are striking. Regimens incorporating an mTOR inhibitor (MTORI) were associated with a 40% reduction in overall skin cancer incidence, driven largely by reduced SCC rates. Conversely, calcineurin inhibitor (CNI) exposure conferred up to a five-fold increase in risk. Importantly, combining low-dose CNI with MTORI mitigated this risk, reducing skin cancer rates by 32-37% in high-risk patients and those with prior lesions.

Gómez-Tomás *et al* address a crucial clinical question. Despite the profound morbidity and mortality burden of skin cancer in OTR, consensus on immunosuppression strategies for primary and secondary prevention remain elusive, resulting in inconsistent practice.[3] Randomised trials support MTORI substitution for CNI,[4,5] particularly after the first SCC, but real world uptake is limited. Patient intolerance and adverse off-target effects have historically led to discontinuation in up to 40%; furthermore any benefit in terms of reduced malignancy risk is offset by increased risk of cardiovascular mortality.[6] Indeed this was highlighted in this study, where only a third of patients who developed skin cancer were commenced on MTORI.

Earlier SCC secondary prevention studies used MTORI as the primary immunosuppressant, requiring relatively high doses to ensure prevention against rejection. Introducing a low-dose CNI alongside an MTORI, leveraging the CNI's well-established superiority in rejection prevention from the ELITE-Symphony trial,[7] may permit lower MTORI dosing, thereby improving tolerability and reducing dose-dependent off-target toxicities while maintaining strong anti-rejection protection. Such a strategy may offer reassurance to OTR, who often place the highest value on safeguarding graft survival and minimising any risk of rejection above all other considerations.[8]

This work provides compelling real-world evidence for the combination of MTORI and low-dose CNI as an approach for primary and secondary SCC prevention. It is constrained by the observational design and its methodological limitations, including potential for unmeasured confounding by indication, and focuses on dermatological outcomes without addressing tolerability or competing risks. However, these findings offer a strong rationale for formal randomised interventional trials. Such studies should evaluate MTORI alongside low-dose CNI-based regimens in high-risk patients, balancing skin cancer prevention against tolerability and graft and patient survival, particularly in transplant recipients who develop a first lesion where the potential for risk reduction may be greatest.

Funding sources: This commentary received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. MJB is funded by a Clinical Career Development Fellowship, supported by the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Science (CIFMS), China (grant number: 2024-I2M-2-001-1).

Conflicts of interest: Nil

Data availability: Not applicable.

Ethics statement: Not applicable.

Patient consent: Not applicable.

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